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On January 31, 2002

TOWNSEND and TOWNSEND and CREW LLP

By: Jay M. Marshall

PATENT

Attorney Docket No.: 021199-000100US

JM
3/12/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Pollack, William

Application No.: 09/660,862

Filed: September 13, 2000

For: METHOD OF MANUFACTURING IMMUNE GLOBULIN

Examiner: V. Ford

Art Unit: 1645

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. WILLIAM POLLACK

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, William Pollack, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently chairman and chief executive officer of Atopix Pharmaceuticals Corporation, the assignee of the subject application.

3. I, Dr. Pollack, graduated from the Imperial College of Science and Technology at London University with a B.Sc degree in physiology and biochemistry. I received a M.Sc degree in chemistry and physics from the St. Georges Hospital Medical School at London University and a Ph.D. in immunology and immunochemistry from Rutgers University. A copy of my curriculum vitae is attached hereto as Exhibit A.

4. I am the named and true inventor of the above-referenced patent application. I have read and am familiar with the contents of the patent application. In addition, I have read the final Office Action, dated November 2, 2001, received in the present case. It is my understanding that the Examiner believes that the Zolton *et al.* patent, U.S. Patent Number 4,597,966, anticipates the manufacturing method of the present invention. It is also my understanding that the Examiner believes that Zolton *et al.* in combination with either Cheung *et al.*, *Annals of Allergy*, Volume 50, March 1983, 155-160, Sirna, U.S. Patent No. 5,908,827, or Thomas, U.S. Patent No. 4,089,944 makes the invention of the present application obvious.

5. With this application, I claim a method of manufacturing a highly purified IgG4 immune globulin preparation. The method comprises the steps of adjusting

plasma to a pH of about 6.5 and a conductivity of between 3.5-6 millisiemens, and contacting the plasma with an anion exchange resin followed by a cation exchange resin to obtain a final effluent that comprises IgG4 essentially free of other IgG subtypes.

6. The Zolton method, unlike the method of the present application, does not result in an immunoglobulin preparation comprising IgG4 that is essentially free of other IgG subtypes. Zolton's method, instead, results in a purified stable IgG gamma globulin preparation containing all IgG subtypes including IgG1, IgG2, IgG3, and IgG4. In contrast, the present application provides a method of producing a purified IgG4 preparation free from IgG1, IgG2 and IgG3. Zolton's patent teaches a stabilized preparation of IgG (including all subtypes). The present application teaches a method of fractionating IgG into its various subtypes. It is neither suggested nor taught in the Zolton patent that the Zolton purification method results in pure IgG4 (free of all other subtypes), nor, in my opinion, could the purification system described in Zolton result in pure IgG4 free of other IgG subtypes.

7. Zolton's purification method utilizes a QAE-Sephadex anionic resin. In contrast, the present invention uses two resins, an anion exchange resin, e.g., DEAE Sepharose, followed by a cation exchange resin, e.g., CM-Sepharose. The extra fractionation step results in an IgG4 preparation free of other subtypes. Prior to the advent of the present invention, further fractionation of an IgG preparation into a purified IgG4 using chromatographic resins was not known. Again, the present invention provides a facile method of manufacturing IgG4 immune globulin that is essentially free of other IgG subtypes.

8. The purified IgG4 preparation has numerous advantages over an IgG preparation containing all of the IgG subtypes. The purer IgG4 preparation contains less protein and has a higher amount of blocking antibody per unit weight or per unit of protein that is being injected. The intravenous injection of many immune globulin products can lead to reactions that are caused by aggregation and fragmentation of the

immune globulin. The lower protein and higher blocking antibody content of the IgG4 preparation results in a preparation that is safer and more effective than the other less pure IgG preparations that contain IgG1, IgG2 and IgG3 as well as IgG4.

9. Further, the Zolton patent in view of Cheung *et al.*, or Sirna, or Thomas does not make obvious the manufacturing method of the present application, as the secondary references of Cheung *et al.*, Sirna, and Thomas do not address the deficiencies in the Zolton patent.

10. Cheung *et al.* documents a correlation between high IgG4 levels and beekeepers. This correlation, at most, indicates that there may be a role for IgG4 in the protection against anaphylactic reactions. Cheung *et al.* does not teach or suggest how to make a purified IgG4 preparation or even that a purified IgG4 preparation would be more desirable than a IgG preparation containing all of the IgG subtypes including IgG4.

11. Sirna teaches the use of ion exchange chromatography and high-resolution chromatography to extract purified polypeptide from human urine. I would not expect a purification system for the extraction of polypeptide from *human urine* to be relevant for the purification of *blood plasma* and immunoglobulins. Furthermore, the Sirna method utilizes multiple resins along with DEAE Sepharose and CM-Sepharose. Sirna does not teach or suggest the use of DEAE Sepharose and CM-Sepharose for the purification of IgG4 from human plasma.

12. Thomas teaches how to rapidly solubilize an anti-hemophilic factor composition. The Thomas reference does not teach or suggest how to make a purified IgG4 preparation. Furthermore, Thomas does not teach or suggest fractionation of IgG into an IgG4 fraction.

13. In view of the foregoing, it is my scientific opinion that, after reading the above mentioned references, the presently claimed method is novel and

unobvious over the cited art. One of skill in the art would not be motivated to make the purified IgG4 preparations using the method of the present application. Therefore, Zolton *et al.* does not anticipate this invention and Zolton *et al.* either alone or in combination with either Cheung *et al.*, Sirna, or Thomas does not make the invention of the present application obvious.

The declarant has further nothing to say.

Date: 1/28/02 By: William Pollack

William Pollack, Ph.D.

CURRICULUM VITAE OF DR. WILLIAM POLLACK

Education

Imperial College of Science & Technology. (London University, England). B.Sc., A.R.C.S., (Major Chemistry & Physics.)

St. Georges Hospital Medical School. (London University. England). M.Sc., (Physiology & Biochemistry). F.R.C.Path.,(Clinical Laboratory Pathology).

Rutgers - the State University of New Jersey.
Ph.D. (Immunology & Immunochemistry). Dissertation thesis: *"A study of the Factors Affecting the Zeta-Potential and Hemagglutination with Human Iso-Antibodies".*

Relevant Professional Experience

Played a leading role in the development of Ortho Diagnostic Systems from a small division into a $200M independent subsidiary company of Johnson and Johnson. Served as Vice President of Research and Development and a Member of the Board of Directors, responsible for administering a R/D budget in excess of $8M and responsible for the activities of more than 160 individuals, mostly scientists and physicians. Subsequently, at the Purdue Frederick Company, served as Vice President of R/D and Member of the Executive Committee.

Have been responsible for more than 50 new innovative products, including the first immunological pregnancy test and on which all current pregnancy test are based, the first test(s) for hepatitis and various other Human Immune Globulins including those to prevent or treat, Hepatitis, Rubella, Allergies, and Rhesus Disease of the Newborn. In addition, have had considerable manufacturing experience, including cost containment and maximizing gross profit. Also developed a new facility for the manufacture of immune globulins that was based on a novel and vastly simplified process developed under my direction.

Received the Albert and Mary Lasker Award for basic research in Antibody-Mediated-Immune Suppression and for the invention and development of an Immune Globulin to prevent Rhesus Disease of the Newborn, a product (RhoGam™) that has eradicated the disease. In addition, in recognition of this work, received numerous other awards including the John Scott Medal from the City of Philadelphia, The Karl Landsteiner Award from the American Association of Blood Banks, the Joseph Bolivar-DeLee Humanitarian Award of the City of Chicago and the Award from the New York State and the Perinatal Society for Unique Contributions to Maternal and Child Health.

Author of numerous publications, including several contributions to books and a member of many distinguished medical and scientific societies, as well as having served on the Immunological Standards Committee of the World Health Organization.

Professional History

1985-Present	Atopix Pharmaceuticals Corporation. Carlsbad, California, 92008 Chairman & C.E.O.
1981-1985	The Purdue Frederick Co. Norfolk, Conn. 06856 Vice President, R/D Member of Executive Committee.
1956-1981	Ortho Diagnostics Systems, Inc. Raritan, NJ 08869 (A Johnson & Johnson Co.) Vice President and Member of Board of Directors Director of Research.
1954-1956	Royal Columbian Hospital British Columbia, Canada. Director of Blood Band & Clinical Laboratories.
1948-1954	St. Georges Hospital Medical School, London, England
1943-1946	Royal Navy, Honorable Discharge Lieutenant(RNVR),

Academic Appointments

1974-1985	Associate Adjunct Professor. University of Medicine & Dentistry of New Jersey. (Previously Rutgers Medical School)
1968-1981	Associate Clinical Professor of Pathology College of Physicians and Surgeons Columbia University, New York City, NY.

Awards and Honors

1969	Karl Landsteiner Award of the American Association of Blood Banks.
1976	John Scott Award, Philadelphia Board of Directors of City Trusts.
1978	XXXI Annual Gibson Lecturer, Columbia Presbyterian Medical Center, New York City.
1979	Joseph Bolivar-DeLee Humanitarian Award. Chicago, Illinois.
1980	Albert and Mary Lasker Clinical Medical Research Award.
1987	Award from New York State Perinatal Society for Unique Contributions to Maternal & Child Health.
1980-2002	Listed in: Who's Who in America. Who's Who in the World. American Men and Women of Science.

Professional and Honorary Societies

American Association for the Advancement of Science

American Association of Blood Banks

American Association of Immunologists

Harvey Society

New York Academy of Medicine

New York Academy of Science

Sigma Xi

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